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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/008,945	01/20/1998	LINDA G GRIFFITH	20220-0169	6828

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	36

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/088945	Griffith et al
Examiner	**Group Art Unit**
Yao	1657

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1/29/02.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 25-52 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 25-52 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Revi w, PTO-948

☐ Other _____

Office Action Summary

The amendment of 1/29/02 has been entered. The amendment amended claims 27, 35, 36, 44 and 46.

Claims examined on the merits are 25-52 which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 27-34 and 36-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlameus et al in view of Barry et al (5,266,326) and Dionne et al (WO 92/19195) and Bhatnagar (5,354,736) for the type of reasons in the previous office action of 8/1/01.

The claims are drawn to a method and implant for introducing cells into a animal to form tissue. In the method, a cell-polymeric composition is formed by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer, introducing the cell-polymeric composition into an animal, and hardening the polymer into a three dimensional open-lattice structure which entraps water molecules to form a hydrogel containing the dissociated cells. The implant contains the cell-polymeric composition that hardens to form the hydrogel and is suitable for implanting before hardening.

Schlameus et al disclose mixing osteoprogenitor cells with a solution of alginate, gelling the alginate to form microcapsules containing the cells and implanting the microcapsules to regenerate bone (col 3, lines 51-68, and col 4, lines 30-40).

Berry et al disclose (abstract and col 3, lines 40-45) injecting an alginate solution and a calcium chloride solution into intra-articular space following closure of a surgical site, and allowing the alginate to

gel *in situ* to prevent intra-articular adhesions. The alginate solution may contain drugs and other therapeutic agents (col 6, lines 52-55).

Dionne et al disclose (page 4, lines 5-16) forming an implantable vehicle containing cells by immobilizing cells in a hydrogel matrix core and surrounding the core with a jacket or membrane that is permselective and prevents the cells in the core from immunological attack. The core and membrane can be made of the same composition hydrogel (page 9, lines 21-22) and can be alginate cross-linked with calcium ions (page 9, lines 3-6, and page 18, line 10). It is possible for a single, continuous hydrogel matrix to provide both immunoisolation and support or immobilization (page 53, lines 5-24). It is further disclosed (page 18, lines 18-24) that a hydrogel matrix precursor solution can be included but not exposed to polymerizing conditions. In the case of sodium alginate, a hydrogel will form after implantation as calcium ions are scavenged from surrounding tissues.

Bhatnagar discloses (abstract and col 13, lines 45-49) carrying out soft and hard tissue repair by implanting a hydrogel matrix that promotes cell attachment to the matrix and cell migration into the matrix. The hydrogel matrix results in a three dimensional environment that causes cells to differentiate (col 13, lines 50-55). When soft tissue repair is carried out, injection can be prior to gelation and the gel formed in situ (col 13, lines 58-60).

It would have been obvious to omit forming microcapsules and inject the cell-containing alginate solution of Schlameus et al into intra-articular space as suggested by Berry et al to allow *in situ* gel formation to prevent intra-articular adhesions, and as suggested by

Dionne et al disclosing forming an alginate hydrogel containing cells after implantation as calcium ions are scavenged from surrounding tissues as an alternative to forming an alginate gel matrix containing cells and implanting the matrix, and as further suggested by Bhatnagar disclosing forming a hydrogel *in situ* for tissue repair. The disclosure by Berry et al and Dionne et al that drugs or other therapeutic agents can be in the injected alginate solution, would have suggested that the cells of Schlameus et al can be present in the alginate solution when injected to obtain the tissue repair function of the cells in addition to preventing adhesions as disclosed by Berry et al.

Applicant's arguments filed 1/29/02 have been fully considered but they are not persuasive.

It is granted as urged by applicants that Schlameus et al hardens an alginate gel before implanting into an animal. However, when the secondary references and Bhatnagar are considered, it would have been obvious to introduce the cell-containing alginate solution of Schlameus et al into an animal, and then allow the alginate to harden to form a hydrogel containing cells in the animal for the cells to function in replacing bone tissue as disclosed by Schlameus et al.

While Barry et al and Dionne et al are injecting an alginate solution containing a therapeutic agent to deliver the agent, and are not producing tissue, Bhatnagar discloses injecting a polymer solution to form a hydrogel *in vivo* for the purpose of forming tissue (col 13, lines 50-60). Bhatnagar discloses that cells differentiate to a greater extent in a three dimensional environment in contact with surrounding extra-cellular matrix. The hydrogel causes the cells to behave as if the cells

are surrounded by extra-cellular matrix and undergo differentiation. This function of a hydrogel hardened *in vivo* would have been motivation for injecting the cell-containing alginate solution of Schlameus et al and form the hydrogel *in vivo* instead of forming microcapsules from the alginate solution and injecting the microcapsules. The references are combined together, and the invention becomes obvious when all the references are considered together as a whole.

Applicants urge that if the peptides of Bhatnagar are omitted from the hydrogel, there is no indication that cells well continue to exhibit the desired metabolic function when they are no longer encapsulated. However, the present claims do not exclude the peptides of Bhatnagar. Furthermore, the purpose of the peptides of Bhatnagar is to aid attachment of cells to the hydrogel. When the cells are entrapped in the hydrogel when the hydrogel is formed as disclosed by Schlameus et al, there will obviously be no need for the peptides for cell attachment since the cells are entrapped. Entrapment can occur in the same way when hardening occurs *in vivo* as when the hydrogel is formed prior to implanting. The hydrogel of Schlameus et al being in the shape of a microcapsule is obviously not essential for functioning of the cells to form tissue since the hydrogel of Bhatnagar is not in microcapsule form and it serves to provide a three dimensional environment for cell attachment and growth to form tissue.

Claims 25, 26, 28-35 and 37-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlameus et al in view of Nevo et al (4,642,120) and Vacanti et al (5,041,138) and Vacanti et al (J. Ped.

Surg.) for the type of reasons in the previous office action as repeated below.

Claims 25 and 35, and claims dependent thereon, require hardening the cell-polymeric composition to form a hydrogel having a desired anatomical shape before introducing the hydrogel into an animal.

Schlameus et al is described above.

Nevo et al disclose (col 1, lines 5-10 and col 3, lines 62-68) repairing cartilage or bone by implanting a gel containing chondrocytes or bone marrow stem cells.

Vacanti et al ('138) disclose forming a molded matrix containing chondrocytes for implanting to form cartilage (col 3, lines 17-43).

Vacanti et al (J. Ped. Surg.) disclose forming a polymer-cell scaffold for implanting wherein a desired shape of the polymer scaffold may be obtained by solvent casting or compression molding (page 3, right col).

It would have been obvious to form the alginate gel of Schlameus et al into a molded anatomical shape instead of microcapsules as suggested by Nevo et al implanting a gel containing cells that is not in the form of microcapsules and by Vacanti et al ('138) and Vacanti et al (J. Ped. Surg.) disclosing implanting molded scaffolds containing cells. Nevo et al and Vacanti et al ('138) use chondrocytes as the cells implanted, and it would have been obvious to implant these cells for their known cartilage forming function.

Applicants urge that Nevo et al fail to disclose a hydrogel and producing a gel having an anatomic shape prior to implantation . However, the gel formed from a fibrinogen solution as disclosed by Nevo

et al is a hydrogel since the gel contains water. Additionally, the gel must be substantially the shape of the injured site or it would not be pressed into the site. A gel having substantially the shape of the injured site into which it is introduced can be considered to have an anatomic shape since the gel fits into a site where tissue previously existed and needs to be regenerated. Furthermore, it would have been obvious when Vacanti et al ('138) and Vacanti et al (J. Ped. Surg.) to mold the hydrogel of Schlameus et al, as well as that of Nevo et al, into the shape of tissue being replaced. While Vacanti et al ('138) and Vacanti et al (J. Ped. Surg.) produce a fibrous matrix from a synthetic polymer as urged by applicants, this does not lead one to believe that a hydrogel cannot be molded. When the references are considered as a whole, it becomes apparent that forming a shaped hydrogel merely requires hardening the gelling solution in a mold having the desired shape. There is nothing in Schlameus et al to suggest that alginate will gel only when in the shape of a bead.

In regard to applicants argument of one not expecting cells to get adequate nutrition in a macroscopic composition such as an ear, the present claims do not require any anatomic shape of the hydrogel that is sufficiently different from the microcapsules of Schlameus et al to lead one to expect cells entrapped in the shaped hydrogel cannot obtain proper nutrition. An anatomic shape does not have to be that of a whole body part or organ such as an ear, but can be the shape of any tissue to be replaced in the body. This encompasses an infinite number of shapes some of which will not be substantially different from the microcapsules of Schlameus et al.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 872-9306 before final rejection or (703) 872-9307 after final rejection.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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DMN
3/29/02

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1265